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Prophylactic Versus Selective Lidocaine for Early Ventricular Arrhythmias of Myocardial Infarction

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A total of 333 patients arriving within 6 h of the onset of suspected or proven but uncomplicated myocardial infarction were randomized to treatment by either the prophylactic or the selective lidocaine strategy. Patients were monitored for 24 h. The major end points were sustained ventricular tachycardia or fibrillation and emergent adverse effects of lidocaine.

There were four episodes of emergent adverse effects of lidocaine, all in patients treated by the prophylactic strategy (2.4%, p = NS). There were two episodes of nonagonal, sustained ventricular tachycardia or fibrillation, both in patients treated by the selective strategy (1.2%, p = NS). The difference between major end points was 1.2% in favor of the selective strategy (p = NS). There were significant differences in lesser ventricular arrhythmias and lesser lidocaine adverse effects but no difference in mortality rate (selective = 3%, prophylactic = 5%, p = NS). Potentially lethal ventricular arrhythmias occurred only in patients with myocardial infarction. Nonlethal but complex ventricular arrhythmias were rare in patients without infarction. However, toxicity occurred in patients with and without infarction.

The major conclusion of this study is that there is no important overall advantage of either strategy for lidocaine use in such patients. The advantage of one is the risk of the other. The strategy used should be selected for individual patients, and the use of one strategy for all patients would seem inappropriate.

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Lidocaine is widely used for treatment of early ventricular arrhythmias of acute myocardial infarction, however, the most appropriate strategy for administration of the drug is controversial (1). The prophylactic strategy is based on the hypothesis that "warning" arrhythmias do not occur or are undetected before occurrence of lethal ventricular arrhythmias, or are ultimately found in the vast majority of patients with myocardial infarction, or both. Practitioners of the prophylactic strategy cite one clinical trial (2) showing prevention of early ventricular fibrillation, albeit with no change in mortality, to support their approach. That trial is characterized by 1) a high incidence of ventricular fibrillation in the placebo group in which therapy was withheld until "persistent ventricular tachycardia or fibrillation" occurred, and 2) exclusion of all patients started on therapy who did not have a myocardial infarction.

The selective strategy is based on the hypothesis that many of the patients more likely to have potentially lethal ventricular arrhythmias can be identified by "warning" arrhythmias. Practitioners of the selective strategy support their approach by citing a number of studies (3) showing no benefit from the prophylactic strategy and more recent studies (4–6) showing 1) a low incidence of early ventricular fibrillation consequent from uncomplicated myocardial infarction, 2) large proportions of patients without myocardial infarction treated when therapy is very early, and 3) adverse effects more serious and frequent than previously reported.

We report here a randomized clinical trial that began on October 24, 1979 and terminated on August 20, 1986 after randomization of 333 patients. Our trial compares both antiarrhythmic and adverse effects of the prophylactic and selective strategies.

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Methods

Patient selection. Patients were evaluated for the trial when they presented within 6 h of chest pain diagnosed as proven or suspected acute myocardial infarction. Proven myocardial infarction was defined as chest pain *plus* typical Q waves and evolutionary ST-T changes in the electrocardiogram (ECG) or a serial increase in serum creatine kinase (total or MB fraction), or both. Patients were excluded if they were >75 years old, had complex ventricular arrhythmias requiring treatment on arrival, were in advanced heart failure or shock, had a contraindication to lidocaine such as persistent sinus bradycardia (<45 beats/min), liver disease or allergy, had received antiarrhythmic drugs in the previous 24 h or refused consent. Patients gave written consent, and this study and its consent form were approved by the Joint Ethics Committee of the University of Calgary and Foothills Hospital.

Drug administration. On randomization, drug (placebo or lidocaine) was administered in a double-blind manner as a 100 mg intravenous loading infusion given over 3 to 5 min, followed by a 3 mg/min continuous intravenous maintenance infusion. An identical 100 mg intravenous infusion was administered 20 min after the first loading infusion. The dosage was adjusted on a milligram per kilogram basis for those patients <50 or >90 kg. These dosages are based on a pilot study in which serum lidocaine levels were monitored. The same pre- and postrandomization data were collected on all excluded patients between April 1, 1982 and the end of the trial. Arrhythmia and adverse effect data were not obtained for the excluded patients.

Arrhythmia monitoring. Arrhythmia monitoring by staff consisted of bedside and central monitors as previously described (6). The patient's ECG was also monitored by continuous tape recordings with a two channel recorder (Avionics model 445). These recordings were unavailable to the coronary care unit staff and their purpose was accurate arrhythmia quantification. Continuous ECG recordings were analyzed later by a research nurse who was unaware of the treatment strategy.

The staff unblinded treatment on detection of complex ventricular arrhythmias (≥5 ventricular premature beats/min, couplets, runs, ventricular tachycardia, multiform ventricular premature beats or R on T phenomenon). Ventricular tachycardia was defined as five or more successive ventricular premature beats with an average RR interval ≤500 ms, and the same RR interval criterion was applied to ventricular couplets and runs. Sustained ventricular tachycardia was defined as that lasting ≥30 s or requiring transthoracic cardioversion for hemodynamic collapse. R on T was defined as a ventricular premature beat with an RR/QT ratio <1.0. Multiform was defined as two or more forms of ventricular premature beats within 1 h.

After unblinding for one of these rhythms, the protocol required patients receiving placebo to receive lidocaine in an open label fashion (selective strategy). For those patients already receiving lidocaine on unblinding for arrhythmias (prophylactic strategy), therapeutic decisions were individualized by the physician in charge. Other reasons for unblinding included major lidocaine toxicity (see the following section on adverse drug effects), no evidence of infarction, onset of shock, heart failure or other exclusion criterion, withdrawal of consent or death. The period of monitoring was 24 h from the onset of treatment. The two major end points were 1) sustained ventricular tachycardia or fibrillation that was nonagonal and occurred in the absence of pulmonary edema, shock, failure of another major organ system or any other identifiable secondary cause; and 2) emergent lidocaine toxicity (see discussion of adverse drug effects).

Adverse drug effects. Patients were also monitored for adverse effects potentially due to lidocaine (6). Symptoms recorded included confusion, slurred speech, dizziness, numbness of lips or tongue, double vision or tremor. These were classified as minor (requiring no alteration of treatment) or major (serious enough to merit unblinding). The protocol also permitted unblinding for severe and persistent nausea and vomiting or persistent bradycardia ≤45 but >35 beats/min as potential adverse effects of lidocaine. The occurrence of emergent problems such as seizures, loss of consciousness, severe and persistent sinus bradycardia (≤35/min), respiratory arrest or asystole (≥5 s) were also recorded.

Data analysis. Comparison of selective and prophylactic strategies was done by chi-square analysis, Fisher's exact test or by unpaired *t* tests. Standard statistical packages (SPSS and BMDP) were used for these analyses (7,8). Large sample continuity corrected confidence intervals for the difference in proportions (9) were calculated for the two major end points. The null hypothesis for each variable was rejected when p was <0.05.

Results

Comparison of patient groups. A total of 34 prerandomization and 31 postrandomization clinical variables in addition to the study end points were recorded and a selection of these are presented in Tables 1 and 2. With two exceptions, randomization resulted in matching of the two groups. Fewer patients with diabetes were randomized to the prophylactic strategy (Table 1), and slightly more patients randomized to the prophylactic strategy had an anterior infarction (Table 2). Approximately 60% of enrolled patients ultimately had proven myocardial infarction (Table 2). The most common reason for unblinding treatment was distinctly different in the two groups. In the prophylactic strategy group it was adverse effects of lidocaine, and in the selective strategy group it was complex ventricular arrhythmias.

Table 1. Selected Baseline Characteristics in 333 Patients Before Randomization

Characteristic	All Patients		Patients With MI		Patients Without MI	
	Sel n = 165	Pro n = 168	Sel n = 90	Pro n = 100	Sel n = 75	Pro n = 68
	Percent ± SE					
Male	75 ± 3	77 ± 3	81 ± 4	80 ± 4	68 ± 5	74 ± 5
Previous MI	28 ± 3	25 ± 3	23 ± 4	22 ± 4	35 ± 6	29 ± 6
Hypertension	33 ± 4	28 ± 3	34 ± 5	27 ± 4	31 ± 5	29 ± 6
Diabetes	18 ± 3	8 ± 2*	18 ± 4	10 ± 3	17 ± 4	6 ± 3†
Smoker	51 ± 4	56 ± 4	52 ± 5	56 ± 5	49 ± 6	57 ± 6
Rales	17 ± 3	18 ± 3	18 ± 4	18 ± 4	16 ± 4	18 ± 5
S_3	6 ± 2	8 ± 2	7 ± 3	9 ± 3	5 ± 3	7 ± 3
Q waves	15 ± 3	19 ± 3	21 ± 4	23 ± 4	8 ± 3	12 ± 4
Increased heart size	8 ± 2	8 ± 2	6 ± 3	8 ± 3	11 ± 4	7 ± 3
Definite MI at entry	30 ± 4	37 ± 4	52 ± 5	60 ± 5	3 ± 2	3 ± 2
On beta-blocker	19 ± 3	13 ± 3	18 ± 4	10 ± 3	20 ± 5	16 ± 4
On streptokinase	12 ± 3	12 ± 3	20 ± 4	19 ± 4	1 ± 1	1 ± 1
	Mean ± SE					
Onset to arrival (min)	133 ± 6	129 ± 6	135 ± 8	124 ± 8	131 ± 10	137 ± 10
Onset to randomization (min)	357 ± 10	352 ± 10	343 ± 15	318 ± 12	374 ± 14	401 ± 16
Age (yr)	57 ± 1	56 ± 1	57 ± 1	56 ± 1	57 ± 1	56 ± 1
Serum CK (U/liter)	134 ± 19	143 ± 21	171 ± 34	188 ± 35	90 ± 12	79 ± 9
Serum potassium (mmol/liter)	4.1 ± 0.04	4.1 ± 0.04	4.1 ± 0.05	4.1 ± 0.05	4.2 ± 0.05	4.2 ± 0.06

*$p < 0.05$ selective vs. prophylactic; †$p < 0.10$ selective vs. prophylactic. CK = creatine kinase; MI = myocardial infarction; Pro = prophylactic lidocaine strategy; S_3 = third heart sound; Sel = selective lidocaine strategy.

In only one instance did a study end point play a role in death (see discussion of comparison of major study end points). Four of the remaining five deaths in the first 24 h were due to cardiogenic shock or myocardial rupture and one was due to severe dissection of the aortic root. There were seven additional deaths after the first 24 h. The major cause of death included pump failure (congestive heart failure, cardiogenic shock or myocardial rupture) in six of the seven, and was aortic dissection in the remaining case. Thus, there were two deaths in patients without myocardial infarction and both of these were due to acute aortic dissection. Agonal, sustained ventricular tachycardia or fibrillation

Table 2. Selected Postrandomization Characteristics End Points in 333 Patients

Characteristic	All Patients		Patients With MI		Patients Without MI	
	Sel n = 165	Pro n = 168	Sel n = 90	Pro n = 100	Sel n = 75	Pro n = 68
	Percent ± SE					
Termination <24 h	46 ± 4	40 ± 4	60 ± 5	46 ± 5†	29 ± 5	32 ± 6
Terminated for						
Lidocaine toxicity	2 ± 1	17 ± 3*	2 ± 1	17 ± 4*	1 ± 1	16 ± 4*
Ventricular arrhythmias	30 ± 4	11 ± 2*	49 ± 5	16 ± 4*	8 ± 3	3 ± 2
Proven MI	55 ± 4	60 ± 4	100	100	0	0
Anterior	—	—	31 ± 5	49 ± 5*	—	—
Heart failure	13 ± 3	11 ± 2	19 ± 4	15 ± 4	5 ± 3	6 ± 3
Hospital mortality	3 ± 1	5 ± 2	4 ± 2	7 ± 3	1 ± 1	1 ± 1
	Mean ± SE					
Peak CK (U/liter)	677 ± 71	773 ± 70	1142 ± 107	1174 ± 94	136 ± 29	207 ± 56
Treatment duration (h)	17.5 ± 0.7	18.0 ± 0.6	15.4 ± 1.0	16.3 ± 1.0	21.2 ± 0.7	20.6 ± 0.7
Days in CCU	3.9 ± 0.3	3.9 ± 0.1	4.5 ± 0.5	4.4 ± 0.2	3.1 ± 0.2	3.2 ± 0.2
Days in hospital	10.8 ± 0.6	11.3 ± 0.6	11.8 ± 0.8	12.0 ± 0.8	9.5 ± 0.7	8.9 ± 0.8

*$p < 0.05$ selective vs. prophylactic; †$p < 0.10$ selective vs. prophylactic. CCU = coronary care unit; other abbreviations as in Table 1.

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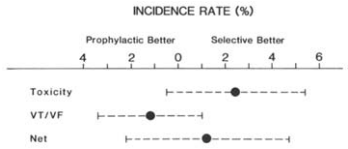

Figure 1. Comparison of the incidence rate of the major end points in the two treatment strategies of this study. Each point is the percent incidence and the horizontal lines indicate the 95% confidence intervals. A point to the right of zero suggests the selective strategy is better than the prophylactic strategy. A point to the left of zero suggests the prophylactic strategy is better than the selective strategy. Net = difference between toxicity and VT/VF; Toxicity = emergent adverse effects of lidocaine; VT/VF = sustained ventricular tachycardia or fibrillation.

occurred in 5 of the 10 patients with death due to pump failure, and in 1 patient who died of aortic dissection; all 6 patients were already receiving lidocaine at the time.

Comparison of major study end points. The differences between the two treatment groups with respect to the major end points of this study are presented in Figure 1. There were four episodes of emergent adverse effects potentially attributable to lidocaine (toxicity), and all occurred in patients randomized to the prophylactic strategy ($p = 0.12$). A 64 year old man receiving a beta-adrenergic blocker developed a heart rate of 33 beats/min and 30 s of apnea after 18 h of treatment; he responded to intravenous administration of atropine. Two hours earlier he had minor symptoms of nausea and slurred speech (code not broken). A 70 year old man with an anteroseptal infarction had a heart rate of 40 beats/min followed immediately by 6 s of asystole and a heart rate of 25 beats/min 75 min after randomization. He was unconscious but responded promptly to chest compression and intravenous atropine. A 59 year old woman had a seizure during administration of the second loading infusion. Treatment was immediately discontinued, but 24 h later she had a second seizure; she had never previously had a seizure. None of these three patients died. The fourth patient, a 65 year old man with anterolateral infarction, became unconscious shortly after the first loading infusion; this event was quickly followed by a seizure, apnea and asystole; resuscitation was unsuccessful. Subsequent review showed a discrepancy in the treatment drug containers indicating that the patient had been given a 1 g container of lidocaine rather than 100 mg.

There were two episodes of sustained ventricular tachycardia and fibrillation (Fig. 1) in the absence of any cause other than an uncomplicated myocardial infarction. Both of these occurred in patients randomized to the selective strategy ($p = 0.50$). A 44 year old man with an anterior myocardial infarction randomized within 116 min of the onset of pain developed rapid ventricular tachycardia degenerating into fibrillation within 9 min of institution of therapy; cardioversion was successful. A 50 year old man with inferior myocardial infarction was randomized within 120 min of arrival and 270 min of the onset of pain. Forty minutes later he had complex ventricular arrhythmias, and 2 min after that developed sustained monoform ventricular tachycardia at a rate of 150 beats/min requiring cardioversion. Neither of these patients died.

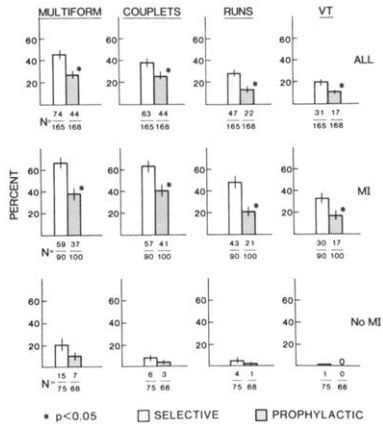

Figure 2. Comparison of the incidence rate (percent of patients) of multiform and successive forms of ventricular premature beats (see Methods) in the two treatment strategies of this study. Vertical lines on the top of the bars are ± SE. Numbers at the bottom of each bar are those used to calculate incidence rate. MI = myocardial infarction; VT = ventricular tachycardia.

Thus, the overall percent incidence of major events in favor of one strategy and its 95% confidence interval is presented as the bottom point ("Net") in Figure 1 and was 1.2% in favor of the selective strategy ($p = 0.68$).

Lesser ventricular arrhythmias. The effects of the two treatment strategies on incidence of lesser ventricular arrhythmias are presented in Figure 2. Similar results were obtained when ventricular arrhythmias were tabulated for each hour of monitoring. The incidence of frequent ventricular premature beats and R on T phenomenon was not significantly different in patients with myocardial infarction randomized to either strategy (not illustrated). Complex ventricular arrhythmias were uncommon in patients without proven myocardial infarction. Fifty patients (30%) randomized to the selective strategy had initial treatment unblinded

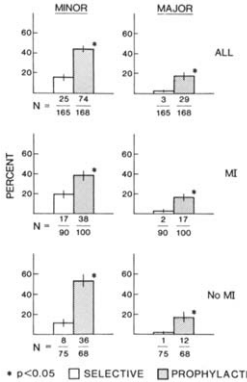

Figure 3. Comparison of the incidence rate (percent of patients) of minor and major adverse effects possibly attributable to lidocaine (see Methods) in the two treatment strategies of this study. Symbols and abbreviations as in Figure 2.

for complex ventricular arrhythmias and 47 of these were started on lidocaine therapy. The remaining three had developed concomitant contraindications to lidocaine therapy. Eighteen patients (11%) randomized to the prophylactic strategy had initial therapy unblinded for complex ventricular arrhythmias. They were treated as follows: nine with no change, five with additional lidocaine, three with continuation of lidocaine and a second drug added and one with discontinuation of lidocaine.

Lesser adverse drug effects. The incidence of minor and major adverse effects potentially attributable to lidocaine are presented in Figure 3. Unlike arrhythmias, adverse drug effects occurred in patients with and without a proven myocardial infarction. Twenty-eight patients (17%) randomized to the prophylactic strategy had their initial treatment unblinded for adverse effects of lidocaine. They were treated as follows: 1 with no alteration, 3 with reduced dosage and 24 with discontinuation of the drug. The three patients (2%) randomized to the selective treatment strategy whose initial treatment (that is, placebo) was unblinded for major adverse effects had the following symptoms: two had nausea and vomiting and one had sinus bradycardia. A breakdown of the type of adverse effect according to whether or not the patient had a proven myocardial infarction is not presented but was similar to that of a previous report (6).

Comparison of study patients to selected groups of excluded patients. Data were available on a total of 1,044 excluded patients. The major reasons for exclusion were as follows: 1) >6 h from the onset of pain without another exclusion, 29%; 2) missed, 14%; 3) >6 h from the onset of pain with another exclusion, 11%; 4) receiving lidocaine, 10%; 5) >75 years old, 8%; 6) receiving another antiarrhythmic drug, 4%; 7) no consent, 4%; 8) all other single exclusions, 8%; and 9) multiple exclusions, 20%.

In Tables 3 and 4, pre- and postrandomization variables for the patients who were missed or did not consent (185 patients) and for those excluded because they were already receiving lidocaine (102 patients) are presented and compared with those of the 333 randomized patients. For excluded patients, the time from "onset to randomization" was that from onset to arrival in the coronary care unit where the study patients were randomized.

Another difference in pre- and postrandomization variables is that 19 ± 4% of the patients receiving lidocaine underwent cardioversion, compared with 2 ± 1% of randomized patients and 1 ± 1% of patients missed or not consenting ($p < 0.05$). A substantial portion (18 of 22) of these cardioversions were for sustained ventricular tachycardia or fibrillation, which occurred before arrival (12 of 18) or in the emergency room (6 of 18). All 12 out-of-hospital patients and 3 of 6 patients in the emergency room were not started on lidocaine therapy until after cardioversion. The four remain-

Table 3. Selected Baseline Patient Characteristics of Randomized and Two Subgroups of Excluded Patients

Characteristic	Randomized Patients (n = 333)	Excluded Patients: Missed or No Consent (n = 185)	Excluded Patients: On Lidocaine (n = 102)
	Percent ± SE		
Male	76 ± 2	71 ± 3	69 ± 5
Previous MI	27 ± 2	38 ± 4*	24 ± 4
Hypertension	30 ± 3	39 ± 4*	48 ± 5*
Diabetes	13 ± 2	16 ± 3	10 ± 3
Smoker	54 ± 3	51 ± 4	43 ± 5†
Rales	17 ± 2	13 ± 2	21 ± 4
S_3	7 ± 1	10 ± 2	8 ± 3
Q waves	17 ± 2	19 ± 3	26 ± 4†
Increased heart size	8 ± 1	11 ± 2	21 ± 4
Definite MI at entry	33 ± 3	34 ± 3	48 ± 5*
On beta blocker	16 ± 2	24 ± 3*	22 ± 4
On streptokinase	12 ± 2	1 ± 1*	0*
	Mean ± SE		
Onset to arrival (min)	131 ± 5	167 ± 10*	190 ± 37*
Onset to randomization (min)	285 ± 6	388 ± 22*	417 ± 72*
Age (yr)	57 ± 1	59 ± 1*	61 ± 1*
Serum CK (U/liter)	138 ± 14	166 ± 20	206 ± 54
Serum potassium (mmol/liter)	4.1 ± 0.03	4.1 ± 0.05	4.1 ± 0.10

*$p < 0.05$ randomized versus excluded subgroup; †$p < 0.10$ randomized versus excluded subgroup. Abbreviations as in Tables 1 and 2.

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Table 4. Selected Post-Admission Patient Characteristics of Randomized and Two Subgroups of Excluded Patients

Characteristic	Randomized Patients (n = 333)	Excluded Patients: Missed or No consent (n = 185)	Excluded Patients: On Lidocaine (n = 102)
	Percent ± SE		
Proved MI	57 ± 3	62 ± 4	76 ± 4*
Heart failure	12 ± 2	17 ± 3	28 ± 4*
Hospital mortality	4 ± 1	5 ± 2	13 ± 3*
	Mean ± SE		
Peak CK	739 ± 51	752 ± 73	1320 ± 124*
Days in CCU	3.9 ± 0.2	3.7 ± 0.2	4.7 ± 0.3*
Days in hospital	11.1 ± 0.4	11.1 ± 0.7	13.9 ± 0.9*

*$p < 0.05$ randomized vs. excluded subgroup. Abbreviations as in Tables 1 and 2.

ing cardioversions occurred later during hospitalization. One was performed for atrial fibrillation, two were performed during agonal ventricular fibrillation in patients already receiving lidocaine and one was performed for cardiac arrest in a patient not receiving antiarrhythmic drugs.

Discussion

Comparison of patient groups. The randomization process resulted in two very comparable groups of patients receiving the prophylactic and selective strategies. Given that 65 clinical variables were examined in addition to the study end points, one could expect a p value of <0.05 to occur by chance alone in 3 of these variables. It is unlikely that the two differences found affect the findings of this study. Of the two differences found, the site of infarction is potentially important. With respect to the major end points, sustained ventricular tachycardia or fibrillation occurred once each in patients with anterior or inferior infarction, and emergent adverse effects of lidocaine were observed in two patients with anterior infarction and two without infarction. We also analyzed for differences in site of infarction between patients with and without lesser arrhythmias and adverse effects of lidocaine and found none. Finally, site of infarction was obtained from the initial admission ECG, which results in imprecise specification of infarction location.

Comparison of major study end points. The prophylactic strategy resulted in a small (2 to 3%) excess of emergent lidocaine toxicity and the selective strategy resulted in a small (1 to 2%) excess of sustained ventricular tachycardia or fibrillation. There was no difference in mortality. A study with sufficient power to show a statistical difference between the two approaches with respect to the major end points would require that a total of up to 13,000 patients be enrolled and randomized. In our view, such a study is unwarranted because any difference demonstrated would have trivial clinical importance.

On the basis of analysis of the patients excluded from our study, we estimated that these results can be generalized to a substantial number of patients. There are no important differences between the study patients and the patients who were excluded because they were missed or did not give consent. Thus, the study results can be generalized to all of these. They can also be generalized to many of those excluded because they were already receiving lidocaine, because approximately half of these patients had lidocaine therapy started for "prophylaxis" or noncomplex ventricular arrhythmias.

The present study results are different from those of Lie et al. (2), the lone study suggesting a benefit of the prophylactic strategy. This may be partly because our study included more patients with a lower risk of sustained ventricular tachycardia/fibrillation or partly because we assessed lidocaine toxicity more carefully. The difference is probably mostly due to the fact that in the present study treatment with lidocaine was mandated in patients receiving placebo when complex ventricular arrhythmias were detected, whereas in the study of Lie et al. (2) patients receiving placebo were not treated unless "persistent" ventricular tachycardia or fibrillation occurred. Thus, the two studies are not comparable.

Comparison of lesser study end points. As previously pointed out by us (6), lesser adverse effects of lidocaine are common when the prophylactic strategy is used. Importantly, and unlike ventricular arrhythmias, lesser adverse effects (like emergent adverse effects) of lidocaine occur at least as frequently in patients without myocardial infarction as they do in patients with infarction.

Complex ventricular arrhythmias are imperfect for selection of patients with myocardial infarction at risk of sustained ventricular tachycardia or fibrillation (10). However, complex ventricular arrhythmias were infrequent in the patients who did not have a myocardial infarction. This finding is important because patients with chest pain but without myocardial infarction have an extremely low risk (0 of 143 patients in this study) of sustained ventricular tachycardia or fibrillation whereas they are at equal risk for adverse effects of lidocaine.

Potential limitations of study. A lower dose of lidocaine, particularly for the second loading infusion, may have resulted in fewer adverse effects in those treated with the prophylactic strategy. Conversely, however, lowering the dosages may have resulted in more ventricular tachycardia or fibrillation with the prophylactic strategy. Fewer serious adverse effects might have occurred if the infusion rate had been lowered at the first symptom of adverse effects or if plasma lidocaine levels had been used to monitor therapy. Obviously, the latter is not possible in a double blind trial, but in addition, plasma lidocaine levels are not commonly

available as a "stat" procedure nor are they well correlated with adverse effects (6). It should be noted that minor adverse effects of lidocaine are nondescript; 19% of the patients with myocardial infarction receiving placebo in the present study were thought to have minor adverse effects of lidocaine; thus their infusion rate would have been inappropriately lowered if this indicator had been used, perhaps resulting in more ventricular arrhythmias.

The present results and conclusions are unaltered when analysis is limited to the data from those patients with definite myocardial infarction. However, exclusion of patients without myocardial infarction in whom treatment was started is contrary to the principle of "intention to treat" and is a major weakness of the study of Lie et al. (2). Indeed, in the present study, treatment was discontinued as soon as myocardial infarction was excluded, which even optimally took 12 to 16 h. Finally, using the prophylactic strategy only for definite myocardial infarction in this study would have meant not treating about 45% of those at risk for ventricular tachycardia or fibrillation (Table 1).

Even earlier treatment may be more effective. Whereas this statement may be true in the case of a definite myocardial infarction, there are data (5) to show clearly that when this decision is made very early, without benefit of confirmatory tests, the proportion of patients without infarction increases sharply and results in a similar trade-off between antiarrhythmic effectiveness and adverse effects such as those demonstrated in the present trial.

Finally, even if a proponent of the prophylactic strategy rationalizes away all the episodes of emergent adverse effects in the present study (the ultimate in bias and clearly improbable), there is still no significant difference between groups in the incidence of ventricular tachycardia or fibrillation ($p = 0.50$). Sufficient power to show even complete effectiveness of the prophylactic strategy (unlikely) for an event with 1.2% frequency in the selective strategy would require randomization of 13,000 patients. On this basis and the basis of no observed difference in mortality, the wisdom of one strategy for all patients must be questioned.

These results cannot be generalized to more aggressive management of patients presenting early during acute myocardial infarction because only approximately 20% of our patients with infarction received thrombolytic therapy. A randomized trial of lidocaine in such patients may be warranted.

Clinical relevance. The present trial, like two other recent trials (4,5), suggests that adverse effects of lidocaine used prophylactically may offset any benefits, particularly when higher proportions of patients without myocardial infarction are included in this approach (3). The dilemma created by this finding is that the incidence of ventricular fibrillation is greatest early in the course of myocardial infarction (10,11), which is precisely the time when the diagnosis is most uncertain.

The strategy one selects should be determined individually by the clinical circumstances. The prophylactic strategy may be preferable early during the course of a definite myocardial infarction, particularly when rhythm monitoring and capability for resuscitation are uncertain. When the prophylactic strategy is used, lidocaine should be discontinued as soon as possible and in any event after no more than 12 to 24 h. The selective strategy may be preferable later during the course of a definite myocardial infarction, particularly when rhythm monitoring and resuscitation capability are certain and most particularly when the diagnosis of myocardial infarction is in doubt.

The assistance and cooperation of a large number of people were necessary to complete this study. We are grateful to the physicians of the Foothills Hospital who allowed us to study their patients. The study could not have been done without the help of the house staff and nurses who worked in the coronary care unit. Astra Canada supplied the lidocaine used in this study. The following individuals made special contributions to completion of the study: Sharon Copot, RN, Robert Sevick, MD, Elaine Scott, BSc, Darlene Abbott, RN, MSc, Sheila Flavelle, RN, Peter Kleinstiver, MSc, Lynne Fator, RN, Virgil Dais, D Pharm, David Merry, MD and Don Soboleski, MD.

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